

activator protein, which nucleotide sequence encoding the transcriptional repressor or activator protein is operatively linked to a chondrocyte tissue-specific promoter;

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wherein expression of the MDE by chondrocytes is capable of being repressed in the mammal until adulthood, and wherein MDE is capable of being expressed in the mammal during adulthood to a level sufficient to cause degradation of an extracellular matrix component in the joints of the mammal.

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30. (Amended) The transgenic mammal of claim 28, wherein the MDE is constitutively enzymatically active.

31. (Amended) The transgenic mammal of claim 30, wherein the MDE is a constitutively enzymatically active MMP-13.

32. (Amended) The transgenic mammal of claim 31, wherein the MMP-13 comprises the sequence of SEQ ID NO:1 or SEQ ID NO:21.

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35. (Amended) The transgenic mammal of claim 28, wherein the transcriptional repressor or activator binding sequence is a repressor binding sequence.

36. (Amended) The transgenic mammal of claim 35, wherein the

repressor binding sequence is a chimeric tetracycline repressor-Vp16 transcription activator polypeptide binding sequence.

37. (Amended) The transgenic mammal of claim 36, wherein the regulatable promoter is a tet07 promoter.

38. (Amended) The transgenic mammal of claim 37, wherein the regulatable promoter comprises the sequence of SEQ ID NO:2.

40. (Amended) The transgenic mammal of claim 28, wherein the extracellular matrix component degradation results in a phenotypic change or changes selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

41. (Amended) A transgenic mouse or rat, or progeny thereof, whose genome comprises,

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase (MMP) that cleaves Type II

collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a tetracycline-regulatable promoter; and

(b) a nucleotide sequence encoding a transcription activator protein, which transcription activator protein binds to the tetracycline-regulatable promoter, wherein expression of the nucleotide sequence encoding the transcription activator protein is operatively linked to a chondrocyte tissue-specific promoter;

wherein expression of the MMP by chondrocytes is capable of being repressed in the mammal until adulthood, and wherein the MMP is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the transgenic mouse or rat.

42. (Amended) The transgenic mouse or rat of claim 41, wherein the MMP is constitutively enzymatically active MMP-13, the tetracycline regulatable promoter is a tetO7 promoter, the transcription activation protein is a chimeric tetracycline repressor-Vp16 transcription activator polypeptide, and the chondrocyte tissue-specific promoter is a Type II collagen promoter.

43. (Amended) The transgenic mouse or rat of claim 42, wherein the Type II collagen degradation results in a phenotypic change or changes selected from

the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

44. (Amended) A method for producing degradation of an extracellular matrix component in the joints of a transgenic mammal, which method comprises:

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- (a) repressing expression of MDE in a transgenic mammal of claim 28 until adulthood; and
 - (b) activating MDE expression in the transgenic mammal after the mammal has reached adulthood such that the MDE degrades the extracellular matrix component in the joints of the transgenic mammal.

45. (Amended) The method according to claim 44, wherein the extracellular matrix component degradation results in a phenotypic change or changes selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

46. (Amended) A method for producing degradation of an extracellular matrix component in the joints of a transgenic mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 36 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating the MDE expression by withholding the tetracycline or tetracycline analog from the mammal after the mammal has reached adulthood, such that the MDE degrades the extracellular matrix component in the joints of the transgenic mammal.

48. (Amended) The method according to claim 46, wherein the extracellular matrix component degradation results in a phenotypic change or changes selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

49. (Amended) A method for producing degradation of an extracellular matrix component in the joints of a transgenic mouse or rat, which method comprises:

(a) maintaining the transgenic mouse or rat of claim 41 in the presence of tetracycline or a tetracycline analog until adulthood; and

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(b) activating the MMP expression by withholding the tetracycline or tetracycline analog from the mouse or rat after the mouse or rat has reached adulthood, such that the MMP degrades the Type II collagen in the joints of the transgenic mouse or rat.

51. (Amended) The method according to claim 49, wherein the Type II collagen degradation results in a phenotypic change or changes selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

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52. (Amended) A method for evaluating potential of a composition to counteract degradation of an extracellular matrix protein in joints of a mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

- (a) administering the composition to the transgenic mammal of claim 28 in which a phenotypic change has been produced by activation of

expression of the MDE during adulthood of the transgenic mammal;

(b) monitoring the phenotypic change; and

(c) comparing the extent of the phenotypic change in the mammal to which the composition was administered relative to a control mammal in which expression of the MDE was activated without administering the composition,

wherein any less extensive development in the nature or extent of the phenotypic change, or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal indicates the potential of the composition to counteract the phenotypic change.

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53. (Amended) A method for evaluating potential of a composition to counteract degradation of an extracellular matrix protein in joints of a mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) administering the composition to the transgenic mammal of claim

36 in which a phenotypic change has been produced by activating

expression of the MDE by withholding tetracycline or a tetracycline analog during adulthood of the transgenic mammal;

(b) monitoring the phenotypic change; and

(c) comparing the extent of the phenotypic change in the mammal to which the composition was administered to a control mammal in which expression of the MDE was activated without administering the composition,

wherein any less extensive development in the nature or extent of the phenotypic change, or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal indicates the potential of the composition to counteract the phenotypic change.

54. (Amended) A method for evaluating potential of a composition to counteract degradation of an extracellular matrix protein in joints of a mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, collagen degradation, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) administering the composition to the transgenic mouse or rat of